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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,863	02/14/2002	Gholam A. Peyman	42561	6337

7590 02/25/2004

Roylance, Abrams, Berdo & Goodman, L.L.P.
Suite 600
1300 19th Street, N.W.
Washington, DC 20036

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,863	PEYMAN, GHOLAM A.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Amendment and Response/Remarks made in the Amendment, both filed 11/19/03 is acknowledged.

Claims 1-34 are pending. Claims 1-34 are rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 8, 9, 10, 12, 18 and 19 rejected under 35 U.S.C. 102(b) as being anticipated by Zeimer (US Pat. No. 5,935,942).

Zeimer discloses methods and materials for chemically treating a target site by utilizing fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, wherein the liposomes release their contents of fluorescent dyes at a temperature of approximately 41°C without causing thermal damage to tissue (see reference column 3, line 10 through col. 7, line 64); and abstract.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 2, 4-7, 11, 13-17 and 20-34 rejected under 35 U.S.C. 103(a) as being unpatentable over Zeimer (US Pat. No. 5,935,942) in view of Khoobehi *et al.* (US Pat. No. 5,976,502).

Zeimer, as discussed above, teaches methods and materials for chemically treating a target site by utilizing fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, wherein the liposomes release their contents of fluorescent dyes at a temperature of approximately 41°C without causing thermal damage to tissue (see reference column 3, line 10 through col. 7, line 64); and abstract.

According to Zeimer, the method involves co-administering intravenously a fluorescent dye encapsulated within heat-sensitive liposomes and a tissue-reactive agent which is effective to cause chemical tissue damage following its activation; non-invasively heating tissue at a pre-determined anatomical locus within the eye so that the heat-sensitive liposomes leak and release their contents into the blood vessel or sinus at the predetermined locus; exciting the fluorescent dye; visually observing a pattern of fluorescent vasculature which develops at the pre-determined locus; and activating the

tissue-reactive agent disposed within the blood vessel or sinus so that the blood vessel or sinus is chemically damaged to an extent sufficient to occlude the vessel or sinus (col. 3, lines 10-24).

Zeimer teaches that the blood vessel or sinus is selectively and non-invasively heated to a temperature of approximately 41°C by irradiating with a laser beam having a wavelength absorbed by blood (col. 7, lines 53-57). This temperature meets the instantly claimed temperature at least 41°C.

The heat-sensitive liposomes include physiologically compatible constituents, such as dipalmitoylphosphatidylcholine and dipalmitoylphosphatidyl-glycerol phospholipids, that permit preparation of liposomes using art-recognized techniques that release their contents at temperatures above those of the mammalian body temperature, i.e., above 37°C. Upon exposure to temperatures at least about 40°C, above mammalian temperature, release occurs by leakage or seepage of the liposomes contents or by lysis of the liposomes (col. 7, lines 10-20).

Additionally, the laser-targeted occlusion method also comprises co-administration of an anti-inflammatory agent or an antibiotic encapsulated within the heat-sensitive liposomes. Antibiotics include anti-bacterial, anti-fungal, anti-neoplastic and anti-parasitic antibiotics. Anti-neoplastic antibiotics include aclacinomycins, bleomycins, chromomycins, mitomycins and the olivomycins (col. 12, lines 51-59).

Zeimer is deficient only in the sense that he does not explicitly teach a first and second fluorescent dye encapsulated into various temperatures.

Khoobehi *et al.* teach a method of observing blood flow through the eye by injecting a carrier, such as liposomes and blood cells containing the dye, into the blood stream whereby the carrier can contain a single dye or a mixture of different dyes. The mixture can be of a first carrier containing a dye capable of fluorescing when exposed to a laser beam in the visible range and a second carrier containing a dye capable of fluorescing when exposed to a red or infrared laser beam. In addition, the cells can be stained with two different lipophilic dyes where the first dye fluoresces when exposed to a red or infrared laser beam and a second dye fluoresces when exposed to a laser beam in the blue-green spectral range (see reference column 3, line 25 through col. 5, line 5).

Therefore, it would have been obvious to one of ordinary skill in the art to use either a single fluorescent dye or a mixture of different fluorescent dyes as taught by Khoobehi within the methods taught by Zeimer, because Khoobehi explicitly teaches liposomes containing a mixture of dyes which serve to enable the dyes to fluoresce when exposed to various types of lasers (i.e., visible range or infrared-spectral range) and similarly Zeimer teaches a method of chemically treating a target site by utilizing fluorescent dyes in order to visualize patterns of fluorescence. The expected result would be a highly effective method of targeting specific tissue sites and observing carriers, particularly liposomes, as similarly desired by the applicant.

Regarding the instantly claimed temperatures at which the fluorescent dyes are released, it is the examiner's position that a skilled artisan, through routine or

manipulative experimentation, based on the intended purpose, could determine suitable temperature ranges. Applicants have not shown any surprising or unexpected results that accrue from the use of the instant temperatures. The prior art clearly shows the teaching of targeting tissue sites through the encapsulation of fluorescent dyes and tissue-reactive substances by heat-sensitive lipid vesicles. Hence the instant invention is rendered unpatentable over the prior art.

Response to Arguments

Applicant's arguments filed 11/19/03 have been fully considered but they were not found to be persuasive.

Firstly, the Applicants argued regarding the 35 U.S.C. §102(b) anticipation rejection of Zeimer (US 5,935,942) for claims 1, 3, 8-10, 12, 18 &19 stating, "The Action refers generally to two and a half pages of the Zeimer patent, but has not identified each of the claim limitations. Therefore, the Action has not established anticipation of the claims. Zeimer fails to disclose each of the claimed method steps. Zeimer is directed to a method for chemically treating a target site. Zeimer does not *hyperthermally* treat the tissue (as in instant claim 1). Further, Zeimer does not disclose heating the target site to hyperthermally treat the target site for a time sufficient to kill cells in the tissue. Zeimer is directed to the non-invasive heating of the tissue without causing thermal damage to the tissue, which is in direct contrast to the claimed invention which specifically recites the step of applying the heat source to the target site to hyperthermally treat the target site for a sufficient time to kill cells in the tissue. Claim 3 depends from claim 1 to recite that the fluorescent dye is releasable from the liposomes at a temperature that is sufficient to kill cells in the tissue without denaturing proteins in the tissue. As noted, Zeimer heats the tissue in a manner that avoids damaging cells or tissues. Claims 8 and 9 depend on

claim 1, which recite that the heat source is a laser, microwave, infrared or ultrasonic source and that the heat source is a heated fluid source, respectively. Regarding claim 10, Zeimer does not disclose continuing heating the target site at a temperature of at least 41°C for sufficient time to hyperthermally treat the tissue and kill cells in the tissue. For claim 12, which depends on claim 10, Zeimer does not disclose or suggest heating the tissue to a temperature for sufficient time to kill cells in the tissue and where the temperature is below the protein denaturing temperature. Claims 18 and 19 correspond to claims 8 and 9, except for depending from independent claim 10 and are also not anticipated by Zeimer."

These arguments have been thoroughly considered but were not found to be persuasive. Zeimer teaches methods and materials for chemically treating a target site by utilizing fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, wherein the liposomes release their contents of fluorescent dyes at a temperature of approximately 41°C. The Applicant's argument that 'Zeimer does not *hyperthermally* treat the tissue (as in instant claim 1) and that Zeimer does not disclose heating the target site to hyperthermally treat the target site for a time sufficient to kill cells in the tissue' is not persuasive since Zeimer teaches, for instance, at col. 6, lines 12-20, that tissue damage can be caused chemically or thermally such as with a laser beam. Zeimer also teaches, for instance, at col. 7, lines 2-3 that tissue-reactive agents may be photosensitive agents activated by light to produce *tissue damage*. The Applicant's argument that 'Zeimer heats the tissue in a manner that avoids damaging cells or tissues' was also not persuasive since Zeimer does not disclose avoiding complete tissue or cell damage. Zeimer at col. 7, lines 45-64 discloses 'non-invasive heating' being defined as heating 'without causing substantial damage to tissue' and therefore this does not preclude the fact that Zeimer completely avoids cell or tissue

damage since some cell or tissue damage may still be present. Furthermore Zeimer utilizes fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, wherein the liposomes release their contents of fluorescent dyes at a temperature of approximately 41°C by irradiating with laser beams (thermally), as similarly desired by the Applicants. Moreover, Zeimer states at col. 3, lines 10-35 that the fluorescent dyes encapsulated with heat-sensitive liposomes are co-administered with tissue-reactive agents that are effective to cause chemical tissue damage following its activation. Therefore, the art teaches the generic concept of treating tissues, utilizing a similar procedure as instantly claimed.

Secondly, the Applicants argued regarding the 35 U.S.C. §103(a) obviousness rejection of claims 2, 4-7, 11, 13-17 and 20-34 over Zeimer ('942) in view of Khoobehi et al. (US 5,976,502) stating, "Khoobehi does not provide the deficiencies of Zeimer such that the combination of Zeimer and Khoobehi et al. does not render the claims obvious. As disclosed in column 7, lines 58-65 of Zeimer, the non-invasive heating releases the contents of the liposomes "without causing substantial damage to the vasculature or extra vascular interstitial tissue. Zeimer does not disclose the basic concept of the claimed invention of heating the tissue to a temperature and for a time sufficient to hyperthermally treat and kill cells in the tissue. Khoobehi et al. clearly fails to disclose hyperthermally treating tissue, therefore the combination does not render the claims obvious. Claim 2 recites that the fluorescent dye is releasable from the liposome at a temperature of at least 42°C. The action contends that temperature is a matter of choice. As disclosed in the specification, heating the tissue to a temperature of at least 42°C ensures that a sufficient temperature is obtained to thermally treat the tissue. It is known in the art that a temperature of 42°C causes cell damage. Zeimer specifically heats the liposomes at a temperature of 41 °C to avoid damaging the tissue. Zeimer effectively teaches away from heating the tissue to a temperature of at least 42°C and clearly provides no motivation or incentive to do

so. Claims 4 and 5 depend on claim 1. Claims 6 and 7, dependent upon claim 4 to recite the specific bioactive compound. Claim 11 recites heating the target site to a temperature of at least 42°C, which at that temperature is known to cause tissue damage. Claims 13-17 also recite heating the target site to a temperature of at least 42°C. It is not obvious to one of ordinary skill in the art to modify Zeimer to heat the target site to a temperature range of 42°C to 50°C for one to ten minutes as in claim 13. Claim 20 recites the step of introducing a second encapsulated fluorescent dye where the dye is releasable at a temp. of at least 50°C. Zeimer, either alone or in combination with Khoobehi et al. do not suggest the claimed method of maintaining the temperature within a specific temperature range. As noted in the Action, Khoobehi discloses the general concept of introducing more than one dye into the bloodstream. However, Khoobehi et al. fails to disclose a method of introducing a first liposome containing a dye as an indicator of the minimum desired treating temperature and a second liposome containing a dye to provide an indicator of the maximum desired treating temperature. Regarding claims 21-34, in general, Zeimer and Khoobehi both apply the laser to the liposomes to release the dye without causing thermal damage of the cells. The cited art does not disclose the use of different colored dyes (claim 25), phospholipids of claims 26 & 27, or specific bioactive compounds of claims 28-31. In view of the deficiencies of Zeimer and Khoobehi et al., claims 1-34 are not anticipated by or obvious over Zeimer, either alone or in combination with Khoobehi et al."

These arguments have been carefully considered but were not found to be persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Zeimer, as

delineated above, teaches methods and materials for chemically treating a target site by utilizing fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, wherein the liposomes release their contents of fluorescent dyes at a temperature of approximately 41°C without causing substantial thermal damage to tissue. Zeimer is lacking in the sense that he does not explicitly teach a first and second fluorescent dye encapsulated into various temperatures. Khoobehi et al. was relied upon for the teaching of a method of observing blood flow through the eye by injecting a carrier, such as liposomes and blood cells containing the dye, into the blood stream whereby the carrier can contain a single dye or a mixture of different dyes. The mixture, as taught by Khoobehi et al. can be of a first carrier containing a dye capable of fluorescing when exposed to a laser beam in the visible range and a second carrier containing a dye capable of fluorescing when exposed to a red or infrared laser beam. In addition, the cells can be stained with two different lipophilic dyes where the first dye fluoresces when exposed to a red or infrared laser beam and a second dye fluoresces when exposed to a laser beam in the blue-green spectral range (see reference column 3, line 25 through col. 5, line 5). Therefore the deficiencies of Zeimer have been sufficiently resolved by Khoobehi et al.

The Applicant's argument that the instant invention desires 'heating the tissue to a temperature of at least 42°C, which ensures that a sufficient temperature is obtained to thermally treat the tissue. It is known in the art that a temperature of 42°C causes cell damage and that Zeimer specifically heats the liposomes at a temperature of 41 °C to avoid damaging the tissue' was not found to be persuasive since generally,

differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. Furthermore, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, the Applicants have not shown any unexpected results that have been obtained through the instantly claimed temperature ranges. The prior art teaches the generic concept of treating tissues using a similar temperature of approximately 41°C. Furthermore, one of ordinary skill in the art would be well aware of modifying temperatures based on the desired or intended purpose. Moreover, the Applicants argument that in the instant case the 'fluorescent dye is releasable from the liposomes at a temp. of at least 42°C' is also not persuasive since this is a future intended purpose, which without structural limitation, holds no patentable weight. Additionally, the Applicants argument that 'heating the tissue to a temperature of at least 42°C ensures that a sufficient temperature is obtained to thermally treat the tissue' is also not persuasive since it is contradicting to instant independent claim 1, which requires a temperature that is less than 42°C. The prior art teaches a temperature of approximately 41°C and does not teach the avoidance of higher temperatures.

As the Applicant admits, Khoobehi discloses the general concept of introducing more than one dye into the bloodstream. The argument that Khoobehi et al. 'fails to disclose a method of introducing a first liposome containing a dye as an indicator of the

minimum desired treating temperature and a second liposome containing a dye to provide an indicator of the maximum desired treating temperature' was not found to be persuasive since initially, Zeimer discloses administering intravenously a fluorescent dye encapsulated within heat-sensitive liposomes and a tissue-reactive agent which is effective to cause chemical tissue damage following its activation. Khoobehi et al. was relied upon solely for the teaching that it is obvious to one familiar with the art to utilize more than one dye.

The argument that 'Zeimer and Khoobehi both apply the laser to the liposomes to release the dye without causing thermal damage of the cells' is disagreed upon since as noted previously, the method of Zeimer does allow for certain cell or tissue damage and does not entirely avoid it.

Lastly, the Applicants argument that 'the cited art does not disclose the use of different colored dyes, the claimed phospholipids or specific bioactive compounds' was also not persuasive since the prior art clearly discloses utilizing a single dye or a mixture of different dyes (see for example, Khoobehi et al. col. 4, line 63 – col. 5, line 5). Suitable phospholipids are also taught (see Zeimer col. 7, lines 10-15). Hence, in view of the teachings of the prior art, the instant invention is anticipated and is obvious over the prior art and thus is rendered unpatentable over the prior art of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns

February 20, 2004

James M. Spear

JAMES M. SPEAR
PRIMARY EXAMINER
AU 1615